

Neuropsychiatric symptoms in untreated Parkinson's disease

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Abstract: Neuropsychiatric and cognitive symptoms are common in Parkinson's disease (PD) and may precede and exceed motor symptoms as major factors impacting disease course and quality of life. Neuropsychiatric symptoms (NPS) in PD are various and are attributed to pathologic changes within multiple brain regions, to psychological stress, and to adverse effects of dopamine replacement therapy. Sleep disorders and mood symptoms such as apathy, depression, and anxiety may antedate the development of motor symptoms by years, while other NPS such as impulse control disorders, psychosis, and cognitive impairment are more common in later stages of the disease. Few studies report on NPS in the early, untreated phase of PD. We reviewed the current literature on NPS in PD with a focus on the early, drug-naive stages of PD. Among these early disease stages, premotor and early motor phases were separately addressed in our review, highlighting the underlying pathophysiological mechanisms as well as epidemiological characteristics, clinical features, risk factors, and available techniques of clinical assessment.

Keywords: neuropsychiatric symptoms, Parkinson's disease, untreated

Introduction

In Parkinson's disease (PD), in addition to the typical motor symptoms, nonmotor symptoms (NMS) may occur, neuropsychiatric manifestations often being the most common.¹ The premotor phase in PD is dominated by different NMS that are known to have a major impact throughout the course of the disease. A number of clinical subtypes with differing NMS patterns have been established, which feature the early, untreated phase of the disease. This framework ensures that NMS are more readily identified and treated optimally. The phenotypic variants are as follows: park cognitive (predominantly presents with cognitive impairment at an early stage), park apathy (high scores on apathy scales), park depression/anxiety (early manifestation of these symptoms), park sleep (characterized by excessive daytime sleepiness or rapid eye movement behavior disorder), park pain (different pain syndromes dominate the clinical picture), park fatigue (exhibited as an independent and severe symptom), and park autonomic (gastrointestinal, genitourinary symptom dominant, and adrenergic dysfunction dominant) subtypes.² A recent study found that the prevalence of neuropsychiatric symptoms (NPS) in early, untreated PD patients was up to 56%.³ Several prior studies have shown these symptoms to have an adverse impact on patient's everyday activities, quality of life, as well as the burden of their caregivers and the health services.⁴⁻¹² Previous research has also suggested that these symptoms are frequently unrecognized and untreated due to several factors such as the incomplete understanding of mental health problems, illness-specific concerns among patients,

access-to-care issues, and inadequate detection of psychiatric complications by clinicians.^{13–15}

NPS are identified to be integral to PD throughout the course of the disease, often developing in the early, untreated stages, before the onset of classical motor symptoms of PD, suggesting that neurophysiological impairments that cause NPS may already develop in the initial phases of PD.^{3,16–19} In contrast, dopamine replacement therapy (DRT), particularly dopamine agonists that cause hyperdopaminergic states, has been associated with psychosis, impulse control disorders (ICDs), excessive daytime sleepiness, and hallucinations.^{20,21} Hence, the occurrence of NPS in PD patients may frequently be related to potentially additive mechanisms, including psychological reactions to disability, psychiatric symptoms caused by structural brain damage, and adverse effects of DRT. This pathophysiological heterogeneity poses a challenge to the clinician. Moreover, knowledge is still limited about structural brain areas and the neuropathological and pathophysiological changes that may associate with NPS in PD. The main limitation of investigating these symptoms is that NPS are influenced by DRT and often are hardly differentiated from each other because of symptom overlaps.

For this reason, we have excluded studies investigating NPS in PD patients receiving pharmacological treatment. Our present review focuses on NPS in the untreated stages of the disease and separately addresses the premotor phase of the disease and the stage where motor signs are already present.

Search methodology

This is a narrative review. Literature research was undertaken using the database Medline via the PubMed interface. The keywords “neuropsychiatric symptoms”, “Parkinson’s disease”, and “untreated” with the use of the Boolean operators “AND” or “OR” were used to identify relevant studies and reports that examined the association between NPS and PD. In the initial literature search, we exclusively chose these three keywords. In addition, we performed a second literature search using the same electronic database with more specific terms to ensure coverage of all aspects that our review focused on. For this purpose, we established a search strategy using the following terms and their combinations: “apathy”, “depression”, “anxiety”, “impulse control disorder”, “psychosis”, “sleep disturbance”, “cognitive deficit” AND untreated OR “drug naive” AND Parkinson’s disease. We included randomized controlled studies, observational studies, meta-analyses, systematic reviews, and case reports published between 1990 and 2016. We reviewed the existing

information on NPS that can be attributed to the following syndromes in patients with pharmacologically untreated PD: apathy, depression, anxiety, ICDs, psychosis, sleep disturbances, and cognitive deficits. For these syndromes, information on pathophysiology, epidemiology, clinical features, risk factors, and assessment instruments was extracted and formed the basis for this review.

Apathy in untreated PD

Apathy can be defined as a behavioral disturbance of primary loss of motivation that is not attributable to reduced intellectual impairment, emotional distress, or level of consciousness.²² The underlying mechanism of apathy in PD patients is unclear. Positive correlation was found between apathy scores and cerebral metabolism in the inferior/middle frontal gyrus, cuneus, and the insula,²³ and there is evidence that apathy in PD is associated with reduced gray matter density in several brain regions such as the precentral gyrus, the inferior parietal gyrus, the inferior frontal gyrus, and the insula.²⁴ It has also been described that apathy is associated with reduced striatal dopamine transporter levels, independent of depression, suggesting that disruption of dopaminergic innervation in the right caudate nucleus and striatum may contribute to the development of apathy even in early, untreated PD with motor disability already present.²⁵ Moreover, recent findings suggest that combined dopaminergic and serotonergic degeneration, especially within the caudate nucleus, could be a key mechanism underlying apathy in newly diagnosed, untreated PD patients with motor symptoms.²⁶ Therefore, such results underline the fact that the pathogenesis of this symptom is complex and is not exclusively linked to dopaminergic dysfunction.

The prevalence of apathy in patients with PD ranges from 17% to 50%^{3,27–30} overall. The wide range of the reported prevalence values may be attributable to differences between study design, disease severity, and the methods used to detect apathy. Apathy has been identified in untreated, newly diagnosed PD patients with motor symptoms, where the prevalence ranged between 12% and 33%,^{28,31,32} however, such cohorts have not been extensively studied in this regard. Studies show that after excluding patients with depression or dementia, the prevalence of apathy in PD drops to 3%–11%,^{33–36} suggesting that symptom overlaps are important to consider.

A case–control, multicenter study – the ONSET PD study – has shown that apathy can precede the onset of motor symptoms in drug-naïve PD subjects at early stages, the prevalence being 50%.³⁷ In addition, a retrospective study that used interviews performed by telephone found

the frequency of apathy to be 23.7% in the prodromal untreated phase of PD.³⁸

The assessment of apathy is difficult because of overlaps with depressive symptoms and cognitive impairment;^{39,40} nevertheless, there is evidence confirming that apathy in PD also commonly occurs as an independent symptom.⁴¹ A recent study validated the apathy evaluation scale (AES) as a reliable questionnaire for detecting apathy in PD.³²

Apathy should be taken into consideration already in the early phases of PD because it has been associated with reduced quality of life in patients,⁴² increased caregiver burden,^{43,44} altered social relationships,⁴⁵ low cognitive status,⁴⁶ increased motor symptoms, and more severe disability;^{47–50} furthermore, it can easily remain undetected, unless specifically screened for. Therefore, early and accurate identification, especially in untreated, newly diagnosed PD patients, can contribute to optimal clinical management.

Depression in untreated PD

Depression is defined as a low mood state as indicated by feelings of sadness, despair, anxiety, emptiness, discouragement or hopelessness, and aversion to activity that can affect a person's thoughts or feelings, behavior, and sense of well-being.⁵¹

Neurobiological factors associated with the underlying neurodegenerative processes in PD play an important role in the appearance of depressive symptoms and may not represent a reaction to disability only.⁵² Several studies have analyzed the neuroanatomical background of depression in PD, mainly with neuroimaging techniques. These publications report that depressive symptoms in PD are related to decreased hippocampus and amygdala volume^{53,54} and increased brain metabolism in the amygdala.⁵⁵ Bilateral decreases in regional cerebral blood flow of the medial prefrontal cortex is also a common finding in PD patients with depression.⁵⁶ Abnormal functional connectivity of the amygdala, the prefrontal-limbic system, the prefrontal cortex, and the lingual gyrus was associated with depressive symptoms in PD patients;^{57,58} however, a study found intact limbic-prefrontal connections⁵⁴ in a similar group of patients. Furthermore, depression in PD is also related to gray and white matter volume deterioration in the orbitofrontal and temporal regions as well as in the cortical-limbic system.^{59–61} Changes in neuronal systems that are associated with the regulation of mood disturbances, such as dopaminergic, noradrenergic, and serotonergic systems, in limbic and cortical structures might also be involved,⁶² but the exact pathomechanism is yet unknown. Furthermore, depression can manifest as a mood reaction to PD itself and to the progressive disability.

In summary, depressive symptoms in PD can have various etiologies. Interestingly, depression can appear several years before the onset of motor manifestations and use of DRT.³⁷ The strong link between depression and PD is underlined by the increased likelihood of developing PD in a cohort of patients with depression than in controls; therefore, it may also be an independent risk factor for PD.^{17,18,63–66}

Depression is one of the most frequently reported NPS in PD generally;⁶⁷ prevalence varies depending on the diagnostic approach (major or minor depressive disorder and dysthymia), the evaluation of patients, and the study population used. A meta-analysis calculated the prevalence of depression in PD overall, taking into account the different settings and different approaches to diagnosis. The weighted prevalence of clinically significant depression in PD was 35%, more precisely of major depressive disorder was 17%, that of minor depression was 22%, and that of dysthymia was 13%.⁶⁷

A study which assessed the impact of depression in the early, untreated stages of PD with motor symptoms already present found a prevalence rate of 27.6%.⁶⁸ Studies involving untreated PD patients showed that, of the NMS, depressed mood was more frequent 2 years and even 10 years before motor onset, the prevalence being 23.7%–68%.^{37,38}

General risk factors for depression in PD include motor disability,⁶⁹ longer duration of the disease,⁷⁰ predominance of right-sided motor symptoms,⁷¹ akinetic-rigid variant of PD,⁷² presence of other NPS,^{73,74} restless legs syndrome (RLS),⁷⁵ presence of sleep disorders,^{76,77} higher daily doses of levodopa,⁷⁸ younger age,⁷⁸ and female gender.⁷⁹

Since depression in PD has been associated with poorer quality of life and increased caregiver concern,^{68,80,81} it is essential to adequately screen for and correctly treat depression already at the onset of PD. Depressive symptoms are frequently masked by other NPS and motor disturbances, and it can develop at any phase in the course of PD;⁹ therefore, it is difficult to recognize it. For screening, the fourth edition of the DSM-IV diagnostic criteria for major depression, minor depression, and dysthymia in PD has been validated.⁸² Still, one of the greatest challenges in PD remains diagnosing and treating depressive symptoms to the point of remission.

Anxiety in untreated PD

Generalized anxiety disorder (GAD) is characterized by excessive worry and anxiety that are difficult to control, cause significant impairment and distress, and occur on >50% of the days within at least 6 months.⁵¹ GAD in PD is characterized by excessive worry about disease progression, muscle

tension, or everyday worries such as financial concerns. Social phobia in PD is described as fear of social consequences resulting from PD symptoms manifesting in public.⁸³

The exact pathomechanism of anxiety is still unclear; however, dysfunction in the dopaminergic system might be implicated, even in newly diagnosed, never treated PD patients.^{84–86} Tissue reduction in the amygdala and bilateral decreased metabolism in the caudate nucleus may also contribute to the development of anxiety.^{55,87} These symptoms could precede the onset of motor symptoms by as much as 20 years and may be early manifestations during the prodromal phase of PD.^{18,66} In addition, the risk of developing PD was found to be greater in a population with anxiety and correlated with the severity of anxiety according to a recent study.⁸⁸ Moreover, the psychological reaction to the development of motor disturbances should not be neglected.

Anxiety is a common NMS among patients with PD overall, with a prevalence interval between 34% and 65%, GAD being the most frequently diagnosed condition.^{89–91} Other common anxiety disorders described in PD are panic attacks and social phobias.⁹²

In two PD cohorts of drug-naïve subjects with motor symptoms, the prevalence of anxiety (16.4% and 24.6%) was also higher than in non-PD controls.^{3,93} A study examined anxiety in the premotor phase of untreated PD and found a prevalence of 13.3%.³⁸

To assess the severity of anxiety symptoms, several scales are used (eg, State-Trait Anxiety Inventory); however, none of these meet the criteria to be recommended and are classified only as suggested.⁹⁴

Risk factors and predictors reported for anxiety symptoms in patients with PD in general include young-onset PD, higher rates of motor fluctuations, morning dystonia,⁹² severity of PD, postural instability, gait dysfunction, symptom clustering and experience of dyskinesia,⁹⁵ nontremor-dominant motor subtype, depressive symptoms, worst sleep quality, being nonwhite, female gender, and younger age.^{93,96,97}

Similar to other NPS, anxiety symptoms in PD also have a negative impact on the quality of life;⁹⁸ therefore, its timely recognition and adequate treatment are of paramount importance.

ICDs in untreated PD

ICDs are a class of psychiatric disorders characterized by impulsivity, failure to resist a temptation, urge, or impulse that may harm oneself or others.⁵¹ The clinical spectrum of ICDs is extensive; the primary disorders in PD include pathological gambling, compulsive shopping, hyperphagia,

hypersexuality, and punting, as well as compulsive use of dopaminergic medication with consequent dopamine dysregulation syndrome (DDS).^{20,99,100} The occurrence of ICD has been associated with overstimulation of the mesolimbic system by dopamine treatment.^{101–103} Decreases in the binding potential of a dopaminergic tracer in the ventral striatum have been reported in PD patients with pathological gambling phenomena undergoing DRT.¹⁰⁴ In addition, another study of PD gamblers showed a disconnection between the anterior cingulate cortex and the striatum.¹⁰⁵ Furthermore, the development of ICD is somewhat related to a significant loss of gray matter volume in the frontal lobe.¹⁰⁶ In drug-naïve PD patients with motor symptoms, who later on develop ICD, lower baseline dopamine transporter availability in the right ventral striatum, anterior-dorsal striatum, and posterior putamen has been shown.¹⁰⁷ As an adjunct, early dysfunction of the mesocorticolimbic circuits has also been hypothesized to play a role in ICD before dopamine treatment in PD patients.¹⁰⁸

The association between high doses of dopaminergic medications, particularly dopamine agonists and increased risk to develop ICDs, seems evident;^{20,109,110} however, currently available literature deals with PD patients undergoing DRT only. The prevalence of ICDs and related behaviors in treated PD was found to be ranging from 8.1% to 43%.^{20,111,112} With motor symptoms already present, recent data suggest that the frequency of ICD symptoms is as common in patients with early-stage, drug-naïve PD as in healthy controls,^{113,114} the prevalence ranging between 17.5% and 18.5%. As far as we know, the prevalence of ICD in newly diagnosed, untreated PD in the premotor stage has not been studied so far.

The development of these behaviors in general is significantly associated with younger onset of PD, male gender, smoking,^{111,115,116} comorbid psychiatric symptoms and greater functional impairment in PD,¹¹⁷ personal or family history of gambling, and solitary marital status;²⁰ however, the main risk factor for developing impulsive behaviors remains the DRT.

For early detection and screening of ICD, the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease (QUIP) has been recently developed and validated, which appears to be a very sensitive instrument for this particular behavioral disorder assessment.^{118,119}

Taken together, findings so far suggest that ICDs are frequent in PD even before the initiation of dopaminergic medication and they are as common as in healthy controls. Therefore, factors other than PD itself lead to the occurrence of ICDs. Careful identification and active screening of

predictive factors and symptoms are needed; moreover, close follow-up on the behavioral alterations to DRT of patients is needed, as these are not automatically reported to physicians. Besides, treatment is challenging and complex as patients may experience dopamine agonist withdrawal syndrome,^{120,121} hence minimizing this complication is very advisable.

Psychosis in untreated PD

Psychosis is a condition of the mind broadly defined as a loss of contact with reality. Psychotic symptoms in PD include delusions and hallucinations, which are risk factors for dementia and predictors of poor prognosis, mortality, and nursing home placement.^{122–124} In addition, it has been identified as a significant determinant of caregiver burden.⁹⁰

Based on previous studies, hallucinations are mainly associated with dopaminergic agent use (especially dopamine agonists, amantadine, and monoamine oxidase B inhibitors).^{125,126} In addition, in PD, persistent visual hallucinations have been linked to high densities of Lewy bodies in the amygdala and parahippocampus¹²⁷ and have been shown to be associated with dysfunction of the temporal lobe, frontal lobe cingulate cortex, hippocampus, primary and secondary visual cortex, thalamus, precuneus, and cerebellum.^{128–134} Concerning the neural pathways, there is evidence, which indicates that serotonin may also contribute to the pathogenesis of complex visual hallucinations besides dopamine in PD, via involvement of the serotonin 2 receptor.¹³⁵ Historical descriptions of PD from the prelevodopa era suggest that hallucinations may be part of PD itself, especially in the context of depression or dementia.¹³⁶

Visual hallucinations are present in about one-quarter to one-third of PD patients overall, auditory being as much as 20%. Sense of presence and visual illusions affect 17%–72% of the patients, and delusions affect ~5%. Nevertheless, in the early stages of PD with motor symptoms, minor hallucinatory phenomena (presence hallucinations, passage hallucinations, and visual hallucinations) have been described in up to 30% of patients.^{122,137,138} In other studies, psychotic symptoms were very rare in patients with early-stage, untreated PD.^{3,29,93} A very recent study analyzing incident PD patients, already in the premotor untreated phase, also confirmed the hypothesis that the use of dopaminergic drugs is not mandatory for hallucinations to appear in PD,¹³⁹ and 33.3% of patients with minor hallucinations manifested these as a premotor symptom; however, the confirmation of these results is necessary.

The main nonmodifiable risk factor of psychosis is cognitive impairment. Other associated factors include older

age/longer duration of PD, disease severity, presence of daytime somnolence or rapid eye movement (REM) sleep behavior disorders (RBDs), depression, and dysautonomia.^{122,140,141}

Since psychotic symptoms are not always reported voluntarily by patients, clinicians should always ask for such experiences. There are some rating scales in use, but none of them are widely accepted. The Neuropsychiatric Inventory and item 2 of the Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) subscale I can be used for screening. More detailed assessments can be made using specific scales such as Parkinson Psychosis Rating Scale. An MDS Task Force recently reviewed psychosis rating scales used in PD and listed the "recommended" ones for use in PD.¹⁴²

Despite the association between medication exposure and psychosis in PD, the duration and dosage of DRT do not clearly correlate with psychosis;¹⁴³ furthermore, based on the previous debating results mentioned, the etiology of psychosis in PD is complex and needs further investigation. In the early, untreated stages in PD, although psychosis is less frequent than in more advanced disease, better understanding of these phenomena is needed, which will lead to better care and improved quality of life.

Sleep disorders in untreated PD

The most frequent sleep disorders in PD are insomnia, excessive daytime sleepiness, RLS, and RBD.¹⁴⁴

The causes of sleep disturbances are multifactorial, but damage to several brainstem nuclei that are directly involved in the regulation of sleeping mechanisms, which are affected in very early premotor stages of PD,^{145,146} is probably significant. Nigrostriatal dopaminergic degeneration could also play a role in the pathogenesis of RBD but not essential for its development.¹⁴⁷ Abnormalities in primary sleep-regulating centers, some NMS have secondary effect on the quality of sleep, such as nocturia, RLS, and narcoleptic pattern of rapid onset of sleep, which are also important causes of sleep-related morbidity in PD.^{148,149} As causative factors, besides the neurodegenerative processes within sleep regulatory brain circuitries, DRT and concomitant medications (eg, antidepressants) as well as comorbidities or other NMS (such as depression) are proposed.¹⁴⁴ Sleep-related problems are also reported to increase the risk of development of PD in the later life similarly to anxiety disorders and depression^{146,150,151} or RLS,¹⁵² and because they usually precede the classic motor abnormalities of PD by many years, they should be clinically evaluated as a potential marker for PD before its onset.^{153,154} Similarly, sleep dysfunctions occur in untreated

PD as well.^{155,156} These facts suggest that the condition is likely to be related to the underlying dopaminergic deficit rather than the effect of dopaminergic treatment, which seems to be only an aggravating component.

In general, sleep disorders affect up to 75% of patients with PD.¹⁵³ Other studies that have evaluated the prevalence of the various sleep disorders in PD patients reported a wide range of prevalence because of different methods used and different PD stage examinations.^{157–163} A recent study exploring the distribution of sleep quality in untreated PD patients with motor symptoms found that 59.2% of the patients had sleep disturbances and the percentage was even higher in patients treated with DRT.¹⁶⁴ In premotor untreated PD, according to studies, the prevalence of sleep disturbances was 17%–52%.^{37,38}

The presence of sleep problems in PD predicts more NMS, fatigue, depression, and cognitive decline,¹⁵⁹ and as other NPS, they have a significant negative impact on patients' quality of life.¹⁶⁵

For the diagnosis of sleep disturbances, the recommended and validated regular screening questionnaires are as follows: the Pittsburgh Sleep Quality Index (PSQI) and the Medical Outcomes Study (MOS) Sleep Scale; for evaluating daytime sleepiness, the recommended and validated regular screening questionnaires are as follows: the Epworth Sleepiness Scale (ESS), the Inappropriate Sleep Composite Score (ISCS), and the Stanford Sleepiness Scale (SSS).¹⁴⁴ The Parkinson's Disease Sleep Scale (PDSS) has also been validated^{166,167} as a simple screening tool for identifying the various types of nocturnal disabilities that disrupt sleep in PD.

Summing up, sleep disorders often precede the development of motor symptoms in PD. Close follow-up of patients with idiopathic sleep disorders could enable early detection of PD.

Cognitive impairment in untreated PD

Findings from prior studies suggest that initial cognitive decline in PD is triggered by comorbid pathology that occurs with aging, widespread PD pathology, or early diffuse brainstem pathology.^{168–172}

The rate of cognitive decline in the premotor phase of PD compared to controls is similar based on two population-based studies,^{173,174} suggesting that global cognitive dysfunction may not occur in premotor PD. Generally, in PD, ~25% of nondemented patients have mild cognitive impairment (MCI)¹⁷⁵ and up to 80% of all PD patients will eventually develop dementia.¹⁷⁶ Prior studies have shown

that a representative rate (10%–40%) of new, untreated PD patients with motor symptoms have cognitive deficits.^{93,177–179} This wide range might be attributed to many factors including study design, methodology, and definition for MCI in PD. The prevalences of cognitive deficits in the two studies with patients in the premotor untreated phase of PD were as follows: memory complaints 54%, inattention 60%, problems to recall words 32.4%, bradyphrenia 25.8%, and forgetfulness 41.9%.^{37,38}

Patients with PD and cognitive decline have more severe dysfunction in the domains of executive and visuospatial functioning and attention, with lesser involvement of memory and language.¹⁸⁰

Based on preliminary studies, cognitive decline is predicted by older age, male gender, being nonwhite, lower educational level, worse olfaction, more severe motor symptoms, presence of RBD symptoms, and other NPS at baseline.^{93,181–184} Cognition in PD is assessed using the Parkinson's Disease-Cognitive Rating Scale and the Mattis Dementia Rating Scale-2, but there are several other scales, which can be used with the same purpose.^{185,186}

Treatment of PD and its correlation with NPS

Although the mechanisms whereby primary NPS related to PD and NPS related to antiparkinsonian medication affect each other are not fully understood, clinical observations underscore the importance of an optimal personalized clinical management in these patients. In general, patients with dopaminergic therapy are more likely to be bad sleepers, depressed, and with cognitive impairment compared to untreated patients.^{164,187,188} In addition, initiation of DRT is associated with an increase in ICD symptoms, psychosis, and excessive daytime sleepiness. However, a summary of several clinical trials on the effects of DRT in PD suggested therapeutic benefit regarding NPS, mainly depression and anxiety.¹⁵ Practically, the introduction of DRT does not significantly improve most of these symptoms because the majority of NPS does not worsen extensively in the first years of PD regardless of treatment. This may suggest that the neuropsychiatric burden and cognitive deficits in newly diagnosed, untreated PD patients are not high overall compared to more advanced, treatment-influenced disease stages.

Discussion/conclusion

Current data suggest that PD should not be considered as a motor disorder only. In addition to the motor symptoms, the prevalence of NPS in PD is high even in the early, untreated

phases of the disease and is associated with reduced quality of life of patients, increased disability, greater caregiver burden, and higher treatment costs. The most frequent NPS in the untreated phase of PD are those of depression, cognitive impairment, and sleep disturbances. The high heterogeneity of PD and the current descriptions of specific NMS-dominant phenotypes in the early, untreated phase of the disease support the idea of nonmotor subtyping. This may be challenging as PD subtypes are unlikely to be apparent, and there is considerable possibility that these subtypes will overlap throughout the course of the disease and are likely to be present only in a proportion of patients. Identification of such subtypes may ensure that NMS are not missed and may have important implications on the development of subtype-specific therapies. It is still unclear to what extent the etiology of NPS is a result of psychosocial stress factors, the neurodegenerative process of PD itself, or complications of DRT. It seems evident that NPS in PD are most likely multifactorial in origin, the contribution of these factors may differ across disease stages and it is highly influenced by DRT. Several but not all NPS are more common in untreated, newly diagnosed patients with PD compared to the general population, but they also remain relatively stable in the early stages of the disease. In contrast, initiation of DRT and disease progression is associated with increasing frequency of several NPS (Table 1). The prevalence and onset of NPS relative to the manifestation of first PD motor symptoms are not well characterized. Assessing the onset of NPS and NMS in general in the premotor phase is difficult because few patients can report them with sufficient precision. It is usually difficult for subjects to remember whether they had some specific symptoms. Therefore, data cannot be assumed to be entirely exact in this regard. It is uncertain to what extent NPS and cognitive impairment are the result

of the widely distributed neurodegenerative process itself, psychological and clinical factors, or the complication of DRT. Undeniably, the contribution of each factor is probably resulting from a number of simultaneous processes throughout the course of the disease. The early and routine screening for a range of prevalent NPS and their related factors is important to initiate optimal treatment. Therefore, close collaboration and a multidisciplinary, personalized care are needed for the effective treatment of patients with PD. Relatively little is known about the clinical course and prognostic significance of NPS and cognitive impairment in PD; therefore, further studies are needed to better understand NPS and cognition in PD soon after the diagnosis and before DRT introduction.

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Disclosure

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Table 1 Reported prevalence of NPS in various phases of PD

| NPS | Overall in PD (%) | Untreated premotor phase of PD (%) | Untreated motor phase of PD (%) |
|----------------------|-------------------|------------------------------------|---------------------------------|
| Apathy | 17–50 | 24–50 | 12–30 |
| Depression | 35 | 24–68 | 28 |
| Anxiety | 34–65 | 13 | 16–25 |
| ICD | 8–43 | No data | 17–18 |
| Psychosis | 17–72 | 33 | 30 |
| Sleep disturbances | 75 | 17–52 | 59 |
| Cognitive impairment | 25–80 | 26–60 | 10–40 |

Abbreviations: ICD, impulse control disorder; NPS, neuropsychiatric symptoms; PD, Parkinson's disease.

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